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Age-related macular degeneration (ARMD) is a major cause of blindness in the elderly. Unfortunately, no proven form of treatment is currently available for the dry, atrophic form of ARMD seen in more than 90% of patients with this condition. A recent theory suggests that ARMD is associated with damage to the retina caused by free radicals. If this is correct, it is possible that the damage could be prevented or moderated by supplementing the diet with specific antioxidant vitamins and minerals that enhance the body's natural defenses against free radicals. This paper reviews the literature regarding the pathogenesis of ARMD and presents a rationale for its management or prevention by the use of supplemental vitamins and minerals.

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FREE RADICALS AND ANTIOXIDANT SUPPLEMENTATION: A REVIEW OF THEIR ROLE IN AGE-RELATED MACULAR DEGENERATION

By

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Anita van der Hagen was born and raised outside of Lewistown, Montana, on a farm. She graduated from St. Leo's High School in 1986 and went on to do three years of undergraduate study at Eastern Montana College in Billings, Montana. Anita entered Pacific University College of Optometry in Forest Grove, Oregon, in September 1989. She obtained her bachelor's degree in visual science in January 1991 and her doctor of optometry degree on May 23, 1993. After graduation Anita plans to enter a residency program and then a group practice setting.

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FREE RADICALS AND ANTIOXIDANT SUPPLEMENTATION: A REVIEW OF THEIR ROLE IN AGE RELATED MACULAR DEGENERATION

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Abstract

Age-related macular degeneration (ARMD) is a major cause of blindness in the elderly. Unfortunately, no proven form of treatment is currently available for the dry, atrophic form of ARMD seen in more than 90% of patients with this condition. A recent theory suggests that ARMD is associated with damage to the retina caused by free radicals. If this is correct, it is possible that the damage could be prevented or moderated by supplementing the diet with specific antioxidant vitamins and minerals that enhance the body's natural defenses against free radicals. This paper reviews the literature regarding the pathogenesis of ARMD and presents a rationale for its management or prevention by the use of supplemental vitamins and minerals.

Key Words

Age-related macular degeneration, vision, vitamins, minerals, nutrition, free radicals, vitamin E, vitamin C, beta-carotene, zinc, selenium, copper, antioxidant supplements.

In the United States, age-related macular degeneration (ARMD) is the leading cause of blindness for persons over 60 years of age. ARMD exists in two forms: dry and wet. The dry form is characterized by a gradual reduction in central acuity and the presence of drusen. It can progress to the wet form, seen in about 10% of ARMD patients, that is characterized by a rapid reduction in central acuity, choroidal neovascularization, and possible vessel leakage. Wet ARMD is potentially treatable by laser photocoagulation of the choroidal neovascularization, but there is currently no proven form of treatment for dry ARMD.

In recent years, several interesting new theories regarding the pathophysiology of ARMD have been developed. In brief, these theories suggest that light (and other factors) cause the production of free radicals in the outer segments of the photoreceptors. These free radicals are either toxic themselves, or they can cause the production of toxic substances that are shed into the pigment epithelial (PE) cells during the normal sloughing of receptor outer segment components. These toxic products accumulate in the PE cells and are eventually excreted in the form of drusen. As drusen accumulate between the PE cells and the choriocapillaris, they block the exchange of metabolic materials, and the PE cells can no longer function. Without metabolic support from the PE cells, the receptors loose their ability to function and may die.

Two important approaches to preventing or managing ARMD are suggested by this theory. First, it is possible that free radical production can be reduced by shielding the receptors from blue and ultraviolet (UV) light. Light with these wavelengths has a high

amount of energy per quanta, and these high energy quanta are thought to be associated with the production of free radicals.

The second approach to ARMD prevention or management involves bolstering the body's natural defenses against free radical damage. These defenses make use of substances that can quench the free radicals without themselves becoming toxic; examples include vitamins such as C and E, along with enzymes that require minerals such as zinc and selenium for their production. The ability of these compounds and enzymes to quench free radicals suggests that dietary vitamin and mineral supplements might be useful for patients with ARMD or who are at risk for developing the disease.

In this paper, the pathophysiology of ARMD will be reviewed, and a rationale for the use of vitamin and mineral supplementation will be presented.

Free Radicals

Free radicals are molecules that are missing an electron in their outer orbits; this makes them intrinsically unstable and highly reactive.[1] To convert to stable state, a free radical must take an electron from another molecule, and in most cases, this converts the molecule from which the electron was taken to a free radical. The sequential stealing of electrons by free radicals often induces a cascade of biochemical chain reactions that can leave many molecules permanently altered or damaged.

In the body, free radicals are produced naturally in many cellular structures including the mitochondria, lysosomes, endoplasmic reticulum, peroxisomes, and plasma membranes. In addition, various external sources, including light, ionizing

radiation, air pollutants, organic solvents, and cigarette smoke can produce free radicals within the body.[2,3]

Of the many types of free radicals, the most damaging are those derived from oxygen. (Table 1)[1] For example, a superoxide radical can be produced by the addition of an electron to molecular oxygen, and two superoxide radicals can combine with hydrogen to produce hydrogen peroxide. With the addition of an electron to hydrogen peroxide, the highly reactive hydroxyl radical is formed. Then, by acquiring another electron, the hydroxyl radical can be converted to water. Although the water that is the end-product of this chain is not harmful to the body, at several points in the chain electrons must be taken from other molecules. This loss of electrons can damage the molecules from which electrons are taken.

Although not technically a free radical, singlet oxygen can also cause similar damage in the body. Singlet oxygen is produced when molecular oxygen absorbs energy causing the spin of one of the electrons to invert. Singlet oxygen is unstable and can damage molecules as it converts back to normal oxygen. In this way it behaves like a free radical, so it is often grouped together with free radicals in terms of its ability to damage the body.[1]

Insert Table 1 About Here

Free Radical Damage in the Body

Prime targets for free radical damage are the polyunsaturated fatty acids located in cell membranes. This is because the high number of double bonds found in these acids makes their molecules

especially easy to attack. The double bonds are convenient sources of electrons for free radicals to steal, but, as the free radicals quench themselves with electrons from the double bonds, the polyunsaturated fatty acid molecules become lipid peroxyl radicals. These lipid peroxyl radicals can be neutralized by stealing electrons from other polyunsaturated fatty acid molecules, however this creates more lipid peroxyl radicals. The reaction can cascade, consuming valuable polyunsaturated fatty acids and producing damaged molecules until all of the lipid peroxyl radicals are neutralized or are quenched by combining with antioxidants. Antioxidants are part of the body's natural defense against free radicals and are capable of quenching the free radicals without themselves becoming free radicals.

In addition to damaging polyunsaturated fatty acids, free radicals can cause cell damage by denaturing sulfur-containing enzymes and other proteins, and they can damage DNA causing carcinogenic mutagens. For this reason, several theories have linked free radicals with the development of some forms of cancer in humans.[4,5] It has also been proposed that free radical damage is involved in atherosclerosis, heart disease, and cerebrovascular accidents.[6]

Protection Against Free Radicals

Because free radicals can have such a devastating effect on the body, several systems have evolved to provide protection against them. These include the use of antioxidant compounds such as vitamins C and E, beta-carotene, and enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. (Table 2)

Insert Table 2 About Here.

Vitamin C is a water-soluble antioxidant that is capable of quenching superoxide, hydroxyl radicals, and singlet oxygen. Vitamin E is a lipid-soluble antioxidant found in cell membranes; it is capable of quenching singlet oxygen, superoxide, and the lipid peroxyl radical. In cell membranes, it can terminate free radical induced chain reactions involving the unsaturated fatty acids.

Beta-carotene is an orange pigment produced by many plants. It is lipid-soluble and found in the cell membranes of animals where it is an efficient quencher of singlet oxygen and free radicals.[7] Chemically, beta-carotene is a pro-form of vitamin A and can serve as a dietary source for this vitamin. However, even though beta-carotene is an effective antioxidant, vitamin A itself does not share this property.[8]

Enzymes in the body's free radical defense system are also capable of converting free radicals to stable compounds before they can inflict major damage on the cell membranes. For example, superoxide dismutase (SOD) is an antioxidant enzyme that catalyzes the conversion of superoxide radicals to oxygen and hydrogen peroxide. For SOD to function properly, zinc, copper, and manganese mineral cofactors are required in the proper amounts.

After SOD has converted superoxide radicals to oxygen and hydrogen peroxide, glutathione peroxidase (which requires the availability of selenium) and catalase (which requires the availability of zinc and copper) continue the process of detoxifying

the free radicals by converting the hydrogen peroxide to water and molecular oxygen. Glutathione peroxidase is also capable of converting the lipid peroxyl radicals formed in cell membranes to normal lipids; thus, it can stop the membrane damage caused by these free radicals.

In the body, the extent of tissue damage caused by free radicals is determined by the balance between the quantity of free radicals that are generated and the strength of the antioxidant defense system. A variety of conditions can affect this balance. For example, environmental factors such as tobacco smoke, or the use of drugs (e.g., acetaminophen) can generate large quantities of free radicals. The balance can also be affected by poor nutrition that leads to deficiencies in the antioxidant vitamins and/or in the mineral cofactors used by the protective enzymes. In cases of this type, supplemention with vitamins and minerals can potentially be of great value.

Generation of Free Radicals in the Retina

Free radicals are produced in many parts of the body. In the retina, it is likely that they are produced as a result of light absorption by photopigments and/or other materials in the outer segments of the photoreceptors. UV and visible blue quanta seem especially capable of producing free radicals because of the relatively high energies these quanta carry. (Figure 1)

Insert Figure 1 About Here

Several studies have shown a relationship between the amount of short wavelength light to which a person is exposed and the occurrence of conditions like cataracts and ARMD that seem to be associated with free radicals.[8,9,10] For example, a strong association between exposure to blue light over a 20-year period and the incidence of ARMD was found in a study of Chesapeake Bay watermen.[11] In this study it was further suggested that the normal mechanisms used by the retina to protect itself from free radicals produced by the short wavelength light might deteriorate with increasing age of the patient. This would upset the balance between free radical generation and quenching by antioxidants, and could result in the development of ARMD.

The composition and structure of the photoreceptor outer segments make them especially vulnerable to free radical attack. The outer segments contain stacks of membranous discs that are rich in polyunsaturated fatty acids. When the photopigment molecules embedded in these disc membranes absorb quanta, they undergo a conformational change which starts the process of phototransduction. It is possible, however, that not all of the energy carried by the quantum is required to trigger the conformational change. The left-over energy is then available to produce free radicals, such as superoxides, that can damage the unsaturated fatty acids of the photoreceptor membranes.

One of the techniques that receptors use to rid themselves of damaged membrane discs involves regenerating new discs at one end of the outer segment and sloughing packets of older discs into the pigment epithelial cells at the other end.[12,13] In the PE cells, the

phagocytized discs are digested by lysosomal enzymes into recyclable compounds. However, when free radicals have oxidized the unsaturated bonds of the fatty acids in the disc membranes and damaged the molecules, they cannot easily be digested. This is because the damaged molecules do not match the specific digestive enzymes available in the PE cells. As a result, the residues of the damaged molecules build up within the PE cells as lipofuscin granules. When a sufficient amount of this material has accumulated, it is deposited onto Bruch's membrane in the form of a drusen; drusen are one of the earliest and most easily detectable signs of ARMD.

As the lipofuscin and drusen increase, they cause physical and metabolic disruption of the PE cells. In part, this is due to the fact that the drusen physically separate the PE cells from their blood supply in the choroid. (Figure 2) Since the photoreceptors receive their metabolic support from the PE cells, damage to the PE cells ultimately results in damage to photoreceptors as well. The end result of this process is ARMD.

Insert Figure 2 About Here

Strategies for Possible Prevention and Management of ARMD

The theory that links short wavelength light to the production of free radicals in the retina, and to the inability of the PE cells to totally digest the discs phagocytized by them, suggests that ARMD could be prevented or managed in some patients. Two general strategies seem reasonable. First, if the retina could be shielded

from high energy quanta, fewer free radicals would be produced and the available antioxidants in the receptors could quench more of them before extensive damage was done. Second, the ability to quench free radicals could be enhanced by increasing the antioxidant levels in the retina via the use of dietary supplementation.

Following the first approach, all ophthalmic lenses should have a significant ability to absorb UV light. The currently used plastic ophthalmic lens materials are reasonably good UV absorbers, and coatings can be added to glass lenses to increase their ability to absorb UV. In addition, the practice of implanting only UV absorbing intraocular lenses should be continued. UV absorbing ophthalmic lenses could be especially valuable for the elderly who have a reduced ability to quench free radicals. They should also probably be recommended for patients exposed to high UV levels. For normal adults, however, under typical conditions most of the incident UV light is absorbed by the cornea and lens, and therefore does not reach the retina.

Unfortunately, even though the lens and cornea absorb UV reasonably well, they transmit visible blue light which has also been shown to damage the retina.[11] For this reason, it seems prudent to suggest sunglasses that absorb most or all of the visible blue for patients who are exposed to high light levels (e.g., skiers, boaters, etc.), and/or for those who have signs or symptoms of ARMD.[14]

The second approach to preventing or managing ARMD involves enhancing the body's free radical defenses.[14] This can be done by increasing systemic levels of the antioxidant vitamins C and E, beta-carotene, and the trace minerals zinc, copper, manganese, and

selenium that are used by the metalloenzymes that quench free radicals. The human body does not produce these antioxidant vitamins and minerals internally, so it must have a continuous supply of them from either foods in the diet or from supplements. The dietary intake of these vitamins and minerals can directly affect their circulating levels and the activities of the antioxidant metalloenzymes.[15,16]

Use of Antioxidants to Protect the Retina

A variety of studies have demonstrated that the level of antioxidant vitamins and metalloenzymes found in the eye are important in protecting the retina from light damage. For example, rats that were supplemented with vitamin C and exposed to intense light showed less photoreceptor damage than did rats who were not supplemented.[17] The preservation of docosahexaenoic acid in the receptors (the main outer segment fatty acid in rods) suggests that vitamin C acts by inhibiting free radical oxidation of membrane lipids. Vitamin C treatment has also been shown to reduce the number of phagosomes present in the PE cells after light exposure. This suggests that vitamin C interrupts the formation of damaged photoreceptor components, probably by its ability to quench free radicals.[18]

Studies with vitamin E and with beta-carotene suggest that these compounds also have antioxidant properties in the retina. Monkeys placed on vitamin E deficient diets developed a macular degeneration characterized by focal disruption of the photoreceptor outer segments,[19] and rats fed a vitamin E poor diet accumulated more lipofuscin in their PE cells than did animals on diets with

adequate vitamin E levels.[20] Hess, et al., also found a decrease in retinal light damage in young rats when they were given supplements of vitamin E or beta-carotene.[21] In humans, the consumption of fruits and vegetables that are inherently rich in beta-carotene has been shown to have an inverse correlation with the incidence of ARMD.[22]

Antioxidant metalloenzymes also play an important role in protecting the retina from light damage. For example, a high concentration of selenium that is used by the enzyme glutathione peroxidase is found in PE cells.[23] This enzyme has significant antioxidant properties, and reduced activity levels have been associated with the development of ARMD in humans.[24]

Another antioxidant metalloenzyme, catalase, uses zinc as a cofactor, and the enzyme has been found to be more active in the PE cells than in any other ocular tissues. The enzyme is especially interesting because its activity decreases during the sixth to ninth decades of human life when lipofuscin accumulation in the PE cells and ARMD frequency increase.[25] In addition, it has been found that the decrease in catalase activity is more pronounced in older patients with ARMD.[25]

In addition to being a component of the antioxidant enzymes catalase and superoxide dismutase, zinc is also a cofactor for the lysosomal enzyme alpha-mannosidase that is found in PE cells. The activity of this enzyme decreases with age, but supplemental zinc can significantly reactivate it.[26] It has been proposed that lipofuscin accumulates in the PE cells as a result of inefficient or insufficient lysosomal enzymes, and this results in the formation of

drusen. If this is correct, and if zinc can reactivate the enzyme, a strong case can be made for zinc supplementation in patients who have ARMD or who are at risk for developing it.

Supplementation with Antioxidants

The literature describing free radical effects on the visual system suggests that it would be prudent for all patients, especially those over 50, to maintain high levels of antioxidant vitamins and minerals. Unfortunately, nutritional surveys in the United States have found that many older people do not have adequate dietary intakes of these substances.[27] It is possible that these deficiencies might increase their risk of developing a free radical-based disease such as ARMD, but it is very hard to change the lifelong dietary habits of people, especially the elderly. For this reason, supplementation with antioxidant vitamins and minerals might be desirable for these patients in order to maintain their antioxidant defenses at optimum levels.

Newsome, et al., investigated the value of antioxidant supplementation specifically for ARMD patients.[28] They gave ARMD patients supplemental oral zinc sulfate over a two-year period and found that the supplemented patients had significantly less vision loss than did controls. Objective evaluations of the patients' macular photographs taken before and after supplementation showed that the zinc treated group either remained stable or had less of an increase in visible drusen than did the control group.

The work by Newsome and others has inspired a number of additional studies designed to investigate the use of antioxidant supplementation. Many of these studies are in progress or are just

about to get underway, so it will be several years before they can provide definitive data on the relationship between ARMD and supplementation.

In one just completed study, 192 ARMD patients were given antioxidant supplements and 61 control subjects were untreated. After 6 months, 87.5% of the supplemented patients versus 59% of the controls had visual acuities equal to or better than baseline (i.e., showed no deterioration in acuity).[a] Another study, currently underway at eight centers, is designed to evaluate the ability of individual antioxidant vitamins and minerals to retard the progression of ARMD and cataracts. Preliminary results suggest that the antioxidants have value for this purpose.[a]

A multi-center study now being conducted at several Veterans Administration and College of Optometry clinics will also provide information on the relationship between ARMD and antioxidants. In this study, 160 subjects with ARMD will be divided into two groups; one group will receive antioxidant supplements and the other group will receive placebos. Changes in retinal function and appearance will be evaluated over the two-year period of the study.[b]

Still another study, called the Age-Related Eye Disease Study, is also just getting underway. This 10-year study, sponsored by the National Eye Institute, will use 4600 subjects to investigate the predisposing and prognostic factors, as well as clinical courses of patients with ARMD and cataracts. It is quite possible that this study will provide additional theoretical support for the use of antioxidants in the treatment or prevention of ARMD and/or cataracts.[c]

The results of these studies will no doubt clarify the relationship between conditions like ARMD and the need for antioxidant vitamin and mineral supplements, but their results will not be available for several years. What is the appropriate course of action for a patient who now has ARMD or who is showing signs of developing ARMD? Is it possible that supplementation might be appropriate for these patients based on the possibility that the antioxidants could affect the progression of the disease?

Over-The-Counter Antioxidant Supplements

Even though it is not yet definite that antioxidants can help patients with eye problems, several manufacturers have introduced products that are directed toward eye health. These products include: ICAPS-Plus® (La Haye Laboratories, 2205 152nd Avenue NE, Redmond, WA 98052, 800 344-2020), NutriVision™ (Bronson Pharmaceuticals, 4526 Rinetti Lane, P.O. Box 628, LaCanada, CA 91012-0628, 800 235-3200), Ocuguard® (Eye Care Communications Inc., 1241 W. Ninth Street, Upland, CA 91786, 800 247-5731), Ocuvite® (Storz Ophthalmics Inc., 3365 Tree Court Ind. Blvd., St. Louis, MO 63112, 800 325-9929), OCuSOFT® VMS (Ocusoft Inc., P.O. Box 429, Richmond, TX 77406-0429, 800 223-4569), and Spectro-Antioxidants™ (Spectrum Scientific Pharmaceuticals Inc., P.O. Box 2469, Covington, LA 70434, 800 228-2654). The formulations of these products are shown in Table 3. The recommended daily allowances (RDAs) and toxic levels for the vitamins and minerals in the products are also shown for comparison purposes. Comparisons are somewhat difficult, however, because the instructions with several of the products are vague about daily doses.

Insert Table 3 about here.

Because the use of supplements to protect against free radical diseases in the eye is still relatively new, the optimum dosages of each of the vitamins and minerals is unknown. It is interesting to note that although all products list vitamin A among their ingredients, not all of them actually contain vitamin A. Vitamin A is an essential nutrient in the body, but it does not have significant antioxidant properties. Instead of vitamin A, most products probably contain beta-carotene. This substance is called a pro-form of vitamin A because it can be converted to vitamin A in the intestine, but more importantly, beta-carotene itself is a potent antioxidant. This is why it is included in the supplements. It is also interesting to note that the products contain different amounts and forms of zinc, and that not all of the products contain the same substances. Do these differences make one product better than the others? Possibly, but information from additional studies will be needed before this question can be answered definitively.

Conclusion

The theory relating free radical damage to the etiology of ARMD seems sound. The explanations of how antioxidants found naturally in the body or introduced through supplements can mitigate the damage caused by the free radicals also seem sound. Beyond this, the work of Newsome, et al., strongly suggests that for some patients with ARMD the use of zinc can be beneficial. Unfortunately,

the studies needed to more completely define the benefits of antioxidants for the management and/or prevention of free radical diseases like ARMD have not been completed, so it will be several years before the evidence showing the efficacy of antioxidants will be available.

In the meantime, is it appropriate to recommend supplementation to all patients, to those with drusen, to those with exposure to high light levels, or to no patients? The answers to these questions probably require a cost/risk/benefit analysis of the supplements. With respect to cost, retail price of the supplements is about 25 cents per day; with respect to risk, the quantities of vitamins and minerals in the products are well below the toxic levels shown on Table 3, and it is unlikely that toxic levels would be reached if the products are taken as supplements to a normal diet. This leaves the question of benefit. Do the products provide benefits to patients equal to their cost? This is a question each doctor must answer for each individual patient, but at this time it appears reasonable to suggest supplementation to most or all patients pending completion of the studies that will provide definitive information on efficacy.

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Footnotes

a. Personal communication from Randall J. Olson, MD, Department of Ophthalmology, University of Utah School of Medicine, Salt Lake City, UT; October 1992.

b. Personal communication from Diane P. Yolton, PhD, OD, Pacific University College of Optometry, Forest Grove OR 97116; October 1992.

c. Information Page from the Office of Frederick L. Ferris III, MD, Study Chair, National Eye Institute, Washington, DC; August 1992.

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Figure Captions

Figure 1. This figure schematically illustrates how free radicals produced by light can either be quenched by antioxidants or can produce the damage associated with ARMD.

Figure 2. Drusen can separate the PE cells from their blood supply, and this can result in the death of photoreceptors.

Table 1. Active Oxygen Species

Formula	Name
O_2^-	Superoxide radical
$HO_2^\cdot$	Hydroperoxyl radical
H_2O_2	Hydrogen peroxide
$OH^\cdot$	Hydroxyl radical
$ROO^\cdot$	Lipid peroxyl radical
$^1O_2$	Singlet Oxygen

· denotes a free electron

1 denotes an inverted spin on one electron

Table 2. Antioxidant defense mechanisms

Mechanism	Activity
Antioxidant Compounds	
Vitamin C	Water-soluble; quenches free radicals to prevent lipid peroxidation, regenerates vitamin E
Vitamin E	Membrane-bound, lipid-soluble; quenches free radicals to prevent lipid peroxidation and to terminate chain reactions in membranes
Beta-carotene	Membrane-bound, lipid-soluble; quenches free radicals to prevent lipid peroxidation and to terminate chain reactions in membranes
Antioxidant Enzymes	
Superoxide dismutase Requires zinc, copper, and manganese for activity	Converts superoxide radical to hydrogen peroxide
Catalase Requires zinc and copper for activity	Converts hydrogen peroxide to water and molecular oxygen
Glutathione peroxidase Requires selenium for activity	Converts hydrogen peroxide to water and molecular oxygen; reduces lipid peroxyl radicals to normal lipids

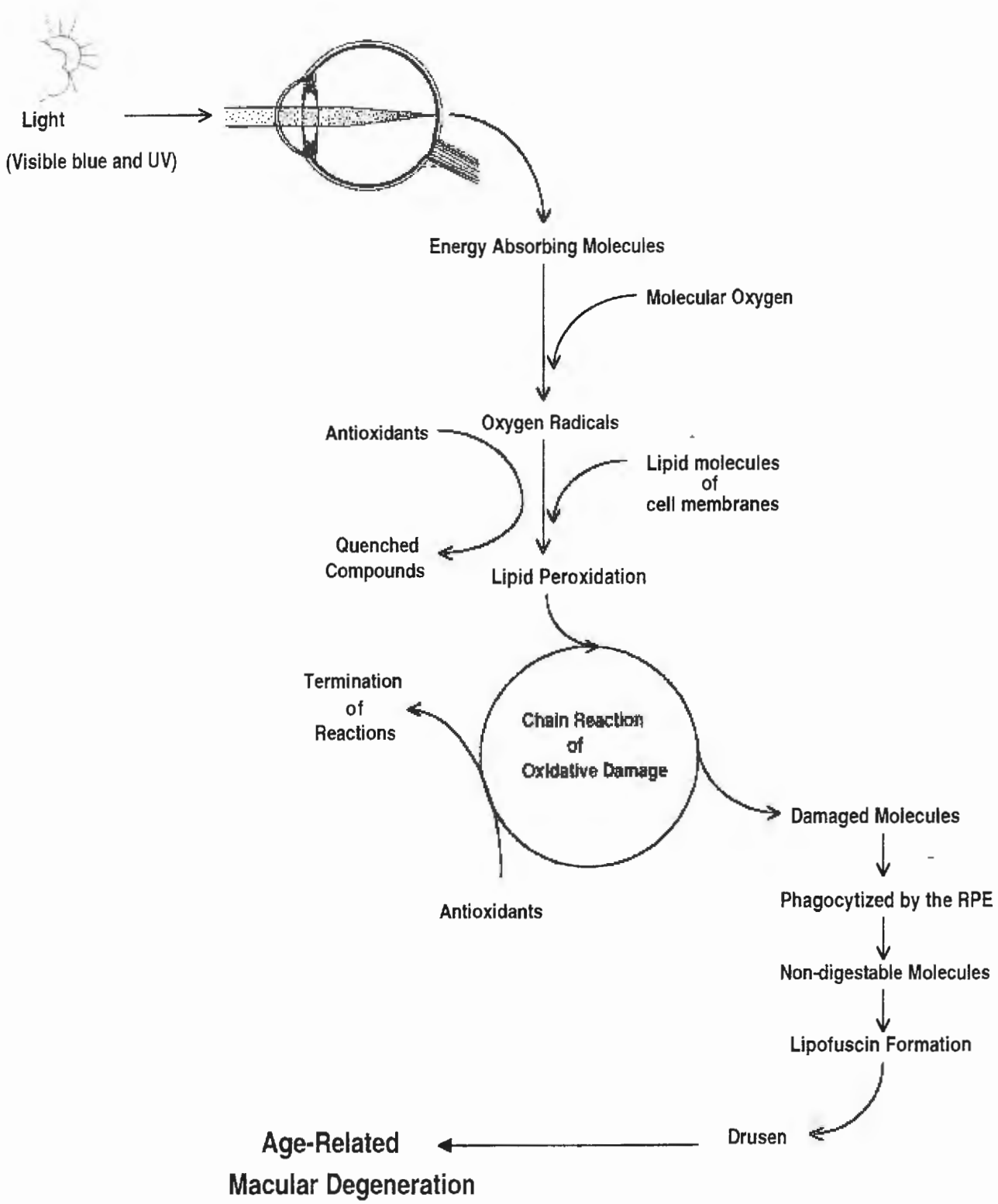
Table 3. Ingredients of several products currently on the market as compared with RDA and toxic levels of these ingredients. Each ingredient is amount per tablet or capsule.

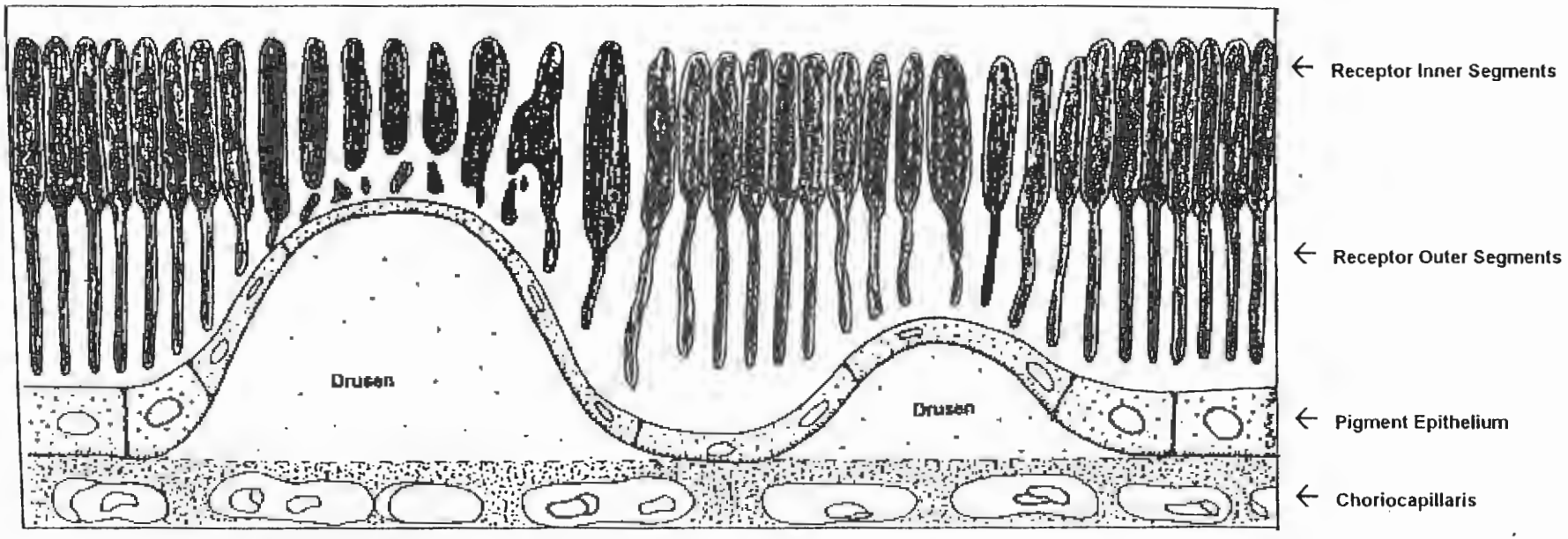
Micro-nutrient (RDA)	Ocuvite®	ICAPS-Plus®	Ocuguard®	Nutri-Vision™	OCuSOFT® VMS	Spectro-Anti-oxidants™	Toxic Levels*
Vitamin C (60 mg)	60 mg	200 mg	375 mg	300 mg	60 mg	400 mg	Prolonged intake exceeding 1g/day
Vitamin E (30 IU)	30 IU	60 IU	100 IU	100 IU	30 IU	200 IU	Greater than 800 IU daily
Beta-Carotene (NE)	5000 IU	6000 IU	10000 IU	5000 IU	5000 IU	5000 IU	Greater than 150,000 IU daily
Zinc (15 mg)	40 mg	30 mg	6.25	30 mg	40 mg	40 mg	Prolonged intake of 150 mg daily
Copper (2 mg)	2 mg	1.5 mg	none	1.5 mg	2 mg	2 mg	Greater than 20 mg daily
Mang-anese (NE)	none	5 mg	none	none	none	none	Greater than 8-9 mg daily
Selenium (NE)	40 mcg	30 mcg	25 mcg	50 mcg	40 mcg	40 mcg	Maximum daily intake is 500 mcg
Riboflavin (1.7 mg)	none	20 mg	12.5 mg	none	none	none	No known toxic level

Table 3. Continued

Other Ingredients	none	none	Bioflavenoids, Taurine, N-acetyl cysteine, Glutathione, Chromium	Chromium	none	Glutathione, Pyruvate
Dose	1 or 2 daily	1 or 2 daily	4 daily	1 or 2 daily	1 or 2 daily	1 or 2 daily

* Shils ME, Young VR, eds. Modern Nutrition in Health and Disease, 7th ed. Philadelphia: Lea & Febiger, 1988.
NE = None Established


Light
(Visible blue and UV)
Energy Absorbing Molecules
Molecular Oxygen
Oxygen Radicals
Antioxidants
Lipid molecules
of
cell membranes
Quenched
Compounds
Lipid Peroxidation
Termination
of
Reactions
Chain Reaction
of
Oxidative Damage
Damaged Molecules
Antioxidants
Phagocytized by the RPE
Non-digestable Molecules
Lipofuscin Formation
Drusen
Age-Related
Macular Degeneration


Drusen
Drusen
Receptor Inner Segments
Receptor Outer Segments
Pigment Epithelium
Choriocapillaris